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Growth Hormone, IGF-I, and the Elderly

Clues to Potential Therapeutic Interventions

Clifford J. Rosen, MD

Chief of Medicine, St. Joseph Hospital, Research Professor of Nutrition, University of Maine, Bangor, ME

Recent studies have confirmed that aging is associated with a continuous decline in growth hormone (GH) production and secretion *(1,2)*. However, the putative relationship between musculoskeletal frailty and impaired growth hormone dynamics remains nebulous at best. In part, this is because there are at least three unresolved issues concerning the physiology of the GH-insulin-like growth factor-(IGH-IGF-I) axis that complicate interpretation and application of several recent studies in elderly men and women.

First, there is no consensus as to the most appropriate and clinically relevant method for diagnosing GH deficiency in the elderly. Newer, but more cumbersome sampling and modeling techniques have proven that integrated GH analysis is likely to be the most accurate way of measuring true GH secretion *(2)*. However, this is clearly too impractical and too costly for large scale screening. There exists a plethora of other less expensive tests that have been applied as surrogate measures of GH secretion. These include serum levels of insulin-like growth factor-I (IGF-I) and IGF-I binding protein-3 (IGFBP-3), an IGF-I/IGFBP-3 ratio, serum free IGF-I, urinary GH, and several body composition indices. However, in almost all cases, attempts to correlate musculoskeletal fragility with these indices have proven fruitless, although this may relate as much to the multifactorial nature of osteopenia and sarcopenia as the limited utility and specificity of these surrogates *(3)*.

The advent of recombinant technology (e.g., GH, IGF-I, IGF-I coupled to IGFBP-3) and the synthesis of innovative GH secretatogs, (e.g., growth-hormone-releasing hormone [GHRH], GRP) have led to a vast array of potential anabolic agents. These compounds may provide an unprecedented opportunity for investigators to attempt to forestall some of the inexorable changes associated with frailty in the elderly. However, from an endocrinologic perspective, it is imperative to define whether treatments will be considered within the realm of physiologic replacement (i.e., a growth hormone deficiency state treated conventionally with hormonal replacement) or in a broader sense as pharmacologic therapy (i.e., treatment to enhance anabolic activity independent of endogenous GH secretion). In that same vein, accurate determination of the GH status of an elder being considered for recombinant human growth hormone (rhGH), is certain to be of paramount importance.

Second, although serum IGF-I declines with age and is an often-measured end point for clinical studies, its validity as a marker of anabolic activity remains uncertain. It has been firmly established that IGF-I can be a potent mitogen for numerous tissues principally through activation of the IGF-I receptor. In muscle and bone, IGF-I also plays a central role in tissue differentiation. However, attempts to discern cellular activity from circulating levels of IGF-I have been fruitless, in part because the regulation of circulating IGF-I is multifaceted, and frequently dissimilar from autocrine and/or paracrine control. But, since IGF-I synthesis in the liver is primarily governed by pulsatile GH secretion, serum IGF-I concentrations have been used clinically as a surrogate measure of GH adequacy. Unfortunately, many other factors affect serum levels of IGF-I, particularly in the elderly. For example, studies have shown that macro-nutrients are key regulators of hepatic IGF-I message *(3)*. Also, insulin can acutely control IGF-I bioactivity by acting both at the level of IGF-I synthesis, and by down regulating hepatic production of one major circulating IGF binding protein, IGFBP-1. Finally, other conditions including systemic disorders, catabolic states, physical inactivity, body composition, and thyroxine can alter serum IGF-I concentrations either at the hepatic level or through changes in clearance *(3)*. Indeed, circulating IGF-I may be a better indicator of the nutritional and metabolic status of an individual, than an indirect measure of integrated GH secretion.

Third, anabolic treatment for elders with rhGH or insulin-like growth factor-I (rhIGF-I) is a tantalizing possibility, but still remains both experimental and controversial. Early in this decade, one small study of elderly men with low IGF-I demonstrated that 6 mo of rhGH could enhance lean body mass and improve spinal bone mineral density

Author to whom all correspondence and reprint requests should be addressed: Clifford J. Rosen, Chief of Medicine, St. Joseph's Hospital, Research Professor of Nutrition, University of Maine, Bangor, ME, 04401. E-mail: crosen@maine.maine.edu

(4). Subsequent trials have failed to confirm any major effects from GH treatment on bone mineral density, despite marked increases in serum IGF-I *(5,6)*. Whether GH can improve functional capabilities is also under close scrutiny after a recent randomized-placebo controlled trial reported no effect of rhGH administration on functional parameters *(7)*. Still, rhGH and rhIGF-I can enhance lean body mass and favorably alter body fat distribution and several lipoproteins *(7)*.

Surprisingly, in the elderly, there is virtually no peripheral resistance to rhGH in terms of serum IGF-I. Yet, there are consistent side effects (gynecomastia and carpal tunnel syndrome) from rhGH, which in children and young adults are very uncommon *(5,8)*. Some of these problems could be ameliorated by administration of oral GH secretatogs or systemic IGF-I bound to IGFBP-3. However, the long term consequences of GH or IGF-I therapy in older individuals are still not known. Theoretically, there is considerable concern that chronically high (young normal) levels of IGF-I could increase the risk of neoplastic growth or transformation. Hence, the potential to improve frailty and quality of life in elders with GH or GH secreatatogs requires far more investigation, especially in respect to safety and efficacy.

This symposium was organized with three specific aims:

1. To ascertain the most effective means of assessing the GH/IGF-I axis in elders;
2. To examine current evidence that anabolic factors may be efficacious in treating musculoskeletal frailty in the elderly; and
3. To determine how elements of the GH/IGF axis can affect cellular senescence and to assess whether certain in vitro models can be applied to the study of specific age-related processes. Although much remains to be learned about the relationship between GH and the process of aging, this meeting and the publications that have arisen from it, should help illuminate the path for future basic and clinical investigations.

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